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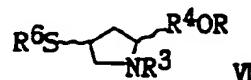
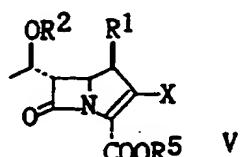
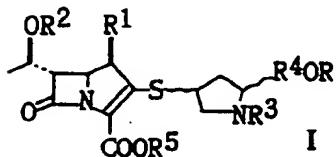
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### (54) Aminoxyppyrrolidinythiocarbapenem compounds.

(57) An antibacterial aminoxyppyrrolidinythiocarbapenem I, its production from the corresponding carbapenem V and thiol VI, its pharmaceutical formulation, and its use for combating bacteria are presented.

The aminoxyppyrrolidinythiocarbapenem (I) and its intermediates (V) and (VI) have the following formulas:

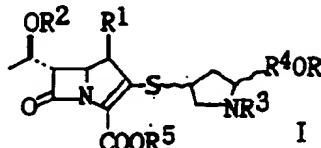


(wherein R is optionally substituted amino; R<sup>1</sup> is hydrogen or 1C to 5C alkyl; R<sup>2</sup> is hydrogen or a conventional hydroxy protective group; R<sup>3</sup> is hydrogen or an imino protective group or imino substituent; R<sup>4</sup> is 1C to 5C alkylene; and R<sup>5</sup> is hydrogen or a conventional carboxy protective group; X is a leaving group; R<sup>6</sup> is hydrogen or a thiol protective group; and wavy lines each shows a bond in R or S configuration and its salts).

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This invention relates to novel carbapenem antibiotics. More specifically, it relates to aminoxyppyrrolidinylthiocarbapenems I and its salts:

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(wherein R is optionally substituted amino; R<sup>1</sup> is hydrogen or 1C to 5C alkyl; R<sup>2</sup> is hydrogen or a conventional hydroxy protective group; R<sup>3</sup> is hydrogen or an imino protective group or imino substituent; R<sup>4</sup> is 1C to 5C alkylene; and R<sup>5</sup> is hydrogen or a conventional carboxy protective group; and wavy lines each shows a bond in R or S configuration).

Several carbapenem antibiotics having pyrrolidinylthio at position 2 are known (e.g., (5R,6S)-2-[1-(1-acetoimidoyl)pyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]carba-2-penem-3-carboxylic acid (CS533), (1R,5S,6S)-2-[(3S,5S)-5-dimethylaminocarbonylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (Meropenem), (1R,5S,6S)-2-[6,7-dihydro-5H-pyrazolo[1,2-a]-1,2,4-triazolium-6-yl]thio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (LJC-10627), (1R,5S,6S)-2-[(3S,5S)-5-methanesulfonylaminomethyl-pyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (Japanese Patent Publication Kokai Showa-63-179876)). However, new potent antibiotics are always demanded to cope with appearance of new resistant strains of bacteria.

The present invention provides useful carbapenem anti-bacterials of Formula I having a pyrrolidinylthio group substituted by an unique aminoxyalkyl moiety at position 2. Compounds of Formula I are found to have excellent antibacterial activity in vitro against Gram-negative bacteria, physico dynamic characteristics, therapeutic properties in treating bacterial infections, as well as excellent chemical and metabolic properties in vivo.

The followings explain some definitions for the compounds of this invention.

In this specification, the substituent in the substituted amino R can be a 1C to 10C monovalent amino substituent (e.g., alkyl, acyl, alkoxy-carbonyl, optionally substituted carbamoyl, alkylsulfonyl, optionally substituted sulfamoyl; especially methyl, acetyl, carbomethoxy, N-methylcarbamoyl, methanesulfonyl, sulfamoyl) and a 1C to 10C divalent amino substituent (e.g., alkylidene, cyclic diacyl; especially ethylidene, phthalyl). R may have one or two of the said monovalent amino substituents or one of the said divalent amino substituents.

The alkyl is a 1C to 10C straight or branched chain saturated hydrocarbon group (e.g., methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 1,2-dimethylbutyl, hexyl, heptyl, octyl).

The alkylene is a straight or branched 1C to 5C divalent hydrocarbon group (e.g., methylene, ethylene, propylene).

The substituent R<sup>3</sup> is an 1C to 19C imino protective group including a 1C to 8C alkyl (e.g., trichloroethyl, methoxyethoxymethyl, tetrahydropyranyl), a 7C to 19C aralkyl (e.g., triphenylmethyl, methoxybenzyl), a 1C to 8C alkylthio, a 6C to 8C arythio (e.g., nitrophenylthio), a 1C to 8C acyl [e.g., 1C to 8C alkanoyl (e.g., formyl, acetyl, chloroacetyl), a 2C to 8C alkoxy carbonyl (e.g., having methyl, ethyl, cyclopropylmethyl, cyclopropylethyl, isopropyl, butyl, isobutyl, hexyl, trichloroethyl, pyridylmethyl, or cyclohexyl as alkoxy), a 8C to 19C aralkoxycarbonyl (e.g., that having benzyl, diphenylmethyl, or nitrobenzyl as aralkoxy), a 7C to 12C aroyl (e.g., benzoyl, nitrobenzoyl)], a 3C to 9C trialkylsilyl, 1C to 5C amidino (e.g., amidino, dialkylamidino), or the like.

The hydroxy protective group is an easily removable 1C to 19C ester forming group [carboxylic acyl, for example, lower alkanoyl (e.g., formyl, acetyl, propionyl, pivaloyl), aroyl, e.g., benzoyl, toluoyl, xyloyl), a 2C to 10C alkoxy carbonyl (e.g., t-butoxycarbonyl, cyclopropoxy-methoxycarbonyl), an 8C to 15C aralkoxycarbonyl (e.g., benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl)], an easily removable 2C to 8C ether forming group (e.g., tetrahydropyranyl, tetrahydrofuranyl, methoxymethyl, methoxyethoxymethyl), or a 3C to 10C hydrocarbysilyl (e.g., trimethylsilyl, triethylsilyl, t-butyldimethylsilyl).

The carboxy protective group can be one of those for synthetic purposes containing 1C to 19 carbon atoms known in this art as those introducable and removable without adverse effect on other parts of the molecule. Representative are ester forming group, e.g., 1C to 8C alkyl (e.g., methyl, methoxymethyl, ethyl, ethoxymethyl, iodoethyl, propyl, isopropyl, butyl, isobutyl, ethoxyethyl, methylthioethyl, methanesulfonyl ethyl, trichloroethyl, t-butyl), 3C to 8C alkenyl (e.g., propenyl, allyl, prenyl, hexenyl, phenylpropenyl, dimethylhexenyl), 7C to 19C aral-

5 kyl (e.g., benzyl, methylbenzyl, dimethylbenzyl, methoxybenzyl, ethoxybenzyl, nitrobenzyl, aminobenzyl, di-phenylmethyl, phenethyl, trityl, di-t-butylhydroxybenzyl, phthalidyl, phenacyl), 6C to 12C aryl (e.g., phnyl, tolyl, diisopropylphnyl, xylyl, trichlorophenyl, pentachlorophenyl, indanyl), 1C to 12C amino (e.g., forming an ester with acetone oxime, acetophenone oxime, acetaldoxime, N-hydroxysuccinimide, N-hydroxyphthalimide), 1-  
10 oxygenated-2C to 15C alkyl (e.g., straight, branched, cyclic, or partially cyclic alkanoyloxyalkyl (e.g., acetoxyethyl, acetoxyethyl, propionyloxymethyl, pivaloyloxymethyl, pivaloyloxyethyl, cyclohexaneacetoxymethyl, cyclohexanecarbonyloxyethyl, 3C to 15C alkoxy carbonyloxyalkyl (e.g., ethoxycarbonyloxyethyl, isopropoxy-carbonyloxyethyl, isopropoxycarbonyloxypropyl, t-butoxycarbonyloxyethyl, isopentylcarbonyloxyethyl, cyclohexyloxycarbonyloxyethyl, cyclohexylmethoxycarbonyloxyethyl, bornyloxycarbonyloxyisopropyl), 2C to 8C alkoxyalkyl (e.g., methoxymethyl, methoxyethyl), 4C to 8C 2-oxacycloalkyl (e.g., tetrahydropyranyl, tetrahydrofuranyl)), 8C to 12C aralkyl (e.g., phenacyl, phthalidyl), 6C to 12C aryl (e.g., phenyl, xylyl, indanyl), 2C to 12C alkenyl (e.g., allyl, prenyl, 2-oxo-1,3-dioxol-4-ylmethyl), or the like.

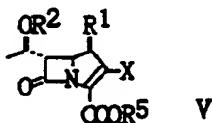
15 The salt at R<sup>6</sup> is preferably a light metal forming a pharmaceutically acceptable ion conventional in the penicillin and cephalosporin fields and belonging to group I to III and period 2 to 4 in the Periodical Table, for example, an alkali metal (e.g., sodium, potassium, lithium), alkaline earth metal (e.g., magnesium, calcium), aluminum, or the like. The ammonium salt at R<sup>6</sup> is preferably a salt with 1C to 12C alkylamine (e.g., trimethylamine, triethylamine, methylmorpholine) or a 4C to 9C aromatic base (e.g., pyridine, collidine, picoline, quinoline). The acid for the acid addition salt at R or R<sup>3</sup> is a pharmaceutically acceptable mineral acid (e.g., nitric acid, hydrochloric acid, sulfuric acid), or 1C to 5C organic acid (e.g., citric acid, succinic acid).

20 These groups can further be substituted.

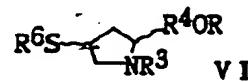
25 Compounds of formula I are all useful for the purpose of this invention. Especially useful are the followings and their alkali metal salts in which the stereochemistry in the pyrrolidine ring is (2S,4R)-or (2S,4S)-: i.e., R is amino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>6</sup> is hydrogen; R is acetyl amino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>6</sup> is hydrogen; R is carbomethoxy-amino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>6</sup> is hydrogen; R is methanesulfonylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens. R<sup>4</sup> is methylene, and R<sup>6</sup> is hydrogen; R is sulfamoylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>6</sup> is hydrogen; R is methylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>6</sup> is hydrogen; and R is ethylidene-amino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>6</sup> is hydrogen.

30 This invention also provides a method for producing Compounds of formula I by condensing a carbapenem of formula V or its reactive derivative with a novel thiol of formula VI (R<sup>6</sup> = H) or its reactive derivative followed by optional deprotection or modification. The carbapenem V and novel thiol VI have the following formulas:

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45 (wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>6</sup> are as defined above, X is a leaving group, and R<sup>6</sup> is hydrogen or a thiol protective group) The leaving group X in the carbapenem V is conventional in the art and can be a 1C to 8C alkanesulfonyloxy (e.g., methanesulfonyloxy, trifluorosulfonyloxy), a 6C to 10C arylsulfonyloxy (e.g., phenylsulfonyloxy, bromobenzenesulfonyloxy, toluenesulfonyloxy), phosphoryloxy (diphenylphosphoryloxy), or a 1C to 8C sulfinyl (e.g., ethylsulfinyl, phenylsulfinyl). The starting carbapenem V or its production is known.

50 This Invention further provides a novel pyrrolidinylthiol VI, the useful intermediate for producing useful carbapenems. The thiol VI is preparable from D- or L-hydroxyproline by combining the following steps in an order suitable for the conventional reactions: 1) Protecting the ring nitrogen (e.g., t-butoxycarbonyl, p-nitrobenzyl oxy carbonyl with the corresponding chloride or anhydride and an organic base), 2) Activating the hydroxy for substitution to thiol (e.g., esterification with alkane or arylsulfonic acid chloride to form a leaving group), 3) Substituting the activated hydroxy with a sulfur function (e.g., triphenylmethylthiol with sodium salt), 4) Reducing the carboxy to methylol (e.g., with alkali metal borohydride), if required after activation (e.g., esterification with lower alkanol), 5) Introducing an amino group to the methylol (e.g., with N-hydroxyphthalimide), if required followed by deprotection (e.g., with hydrazine) or modification at amino as R to form the desired R<sup>4</sup>OR group, and 6) Deprotecting at the ring R, R<sup>3</sup>, or thiol, if required. Preferable R<sup>6</sup> is 1C to 10C alkanoyl (e.g., acetyl, isobutyryl), 7C to 10C aroyl (e.g., benzoyl, toluoyl), or 7C to 19C aralkyl (e.g., trityl, benzhydryl).

55 The carbapenem V and thiol VI are condensed in a conventional manner in an aprotic polar solvent (e.g.,

acetonitrile) in the presence of a tert-ary amine (e.g., diisopropylamine) at a low temperature, for example, -50 to +30°C (preferably -40 to 10°C) for 10 minutes to 10 hours (preferably 30 minutes to 5 hours).

The product is subjected to deprotection, modification at the ring nitrogen, etc. to obtain the desired Compounds of formula I. The deprotection can be done in a conventional manner for producing carbapenem compounds. For example, a p-nitrobenzyl ester as R<sup>5</sup> is sulfonic acid buffer solution by catalytic hydrogenation using palladium sulfonic acid buffer solution by catalytic hydrogenation using palladium on charcoal. Further, some carboxy protective ester group for R<sup>5</sup> (e.g. allyl, isoprenyl, p-methoxy-benzyl, diphenylmethyl) and amino protective carbonate acyl groups in R or imino protective carbonic acyl groups for R<sup>3</sup> (e.g., t-butoxy-carbonyl, allyloxycarbonyl, p-methoxybenzylloxycarbonyl) can be removed using 1 to 20 (preferably 2 to 15) equivalents of a Lewis acid (e.g., aluminum chloride, stannic chloride, titanium chloride) or a carboxylic acid (e.g., trifluoroacetic acid) in an aprotic solvent (e.g., dichloro-methane, anisole, nitromethane) for 1 to 10 (preferably 1 to 5 hours) at -40 to 10 (preferably -30 to 0)°C. A trialkylsilyl hydroxy protective group as R<sup>1</sup> (e.g., trimethylsilyl, triethylsilyl, t-butyldimethylsilyl) can be removed with an aqueous acid (e.g., hydrochloric acid or the like mineral acid).

15 A modification of the ring imino, amidino introduction, is as follows:

Ethylformimidate hydrochloride is added in several portions to a solution of Compound of formula I in a phosphate buffer of pH about 7 under ice cooling while keeping pH 8.5 with 1N-sodium hydroxide.

16 The work up of the reaction mixture is done in a conventional manner in the art to give the free acid, for example, removing unreacted reagent, purifying by crystallization, adsorption and elution, chromatography, lyophilization, etc.

Compounds I show potent antibacterial activity *in vitro* and good physico dynamic properties (e.g., urinary recovery, maximum blood level in mice, and stability to human renal dehydropeptidase 1) as compared with some known carbapenems. For example, Compounds I in which R is methanesulfonylamino (M) or sulfamido (H) show the following percentage improvements over some known carbapenems:

25 vs. Imipenem: twice the antibacterial activity *in vitro* or more against Gram-negative bacteria (e.g., *Escherichia coli* H, *Escherichia coli* SR 5028, *Klebsiella pneumoniae* SR1, *Proteus mirabilis* PR4, *Morgania morganii* SR9, *Enterobacter cloacae* SR233) (M, H), urinary recovery in mice (M:23%, H:44%), and stability against human renal dehydropeptidase-1 (M:53%, H:39%).

30 vs. Meropenem: urinary recovery (M:151%, H:192%), maximum blood level (M:62%, H:92%), protection of mice from *Streptococcus aureus* Smith infection (M:370%, H:1300%), and stability to human renal dehydropeptidase-1 (M:3%, H:13%).

35 vs. CS 533: twice the antibacterial activity *in vitro* or more against Gram-negative bacteria (e.g., *Escherichia coli* H, *Escherichia coli* SR 5028, *Klebsiella pneumoniae* SR1, *Proteus mirabilis* PR4, *Morgania morganii* SR9) (M, H), maximum blood level (M:27%, H:51%), urinary recovery in mice (M:71%, H:99%), and stability to human renal dehydropeptidase-1 (M:63%, H:48%).

40 vs. LJ 10627: twice the antibacterial activity *in vitro* or more against Gram-negative bacteria (e.g., *Proteus mirabilis* PR4, *Proteus vulgaris* CN-329, *Proteus vulgaris* SR3, *Morgan morganii* SR9, *Serratia marsecens* A13880) (M, H).

45 vs. a compound in Japanese Patent Publication Kokai 179876/1988: about twice the activity *in vitro* against *Staphylococcus aureus* SR 77 and *Morgania morganii* SR 9 (M).

Thus, Compounds I are useful as medicines, veterinary drugs, disinfectants, antiperishables, etc., and this invention provides an antibacterial agent containing the compound as an effective component and a method for disinfection by contacting the compound with bacteria.

50 Compound I in which R<sup>5</sup> is an alkali metal is suitable for parenteral administration (e.g., Intravenous Injection, intramuscular injection, drip) and presented in the form of an injection, vials, etc., if required accompanied by a stabilizing and solubilizing agent. The free acid can form an aqueous solution by neutralization before administration. The esters can be used for oral administration as tablets, capsules, granules, powders, etc., for injection as suspension, oily injection, etc., and for external and topical use as a suppository, eye solution, ointment, emulsion, spray, etc. These preparations can be produced using conventional additives in a conventional manner.

55 An effective amount of compound I or its salt is given to an infected subject by way of, e.g., oral or parenteral route, although the latter is more preferable. For parenteral administration, the compound is formulated to afford an aqueous solution or suspension (suitable for e.g., subcutaneous injection, intravenous injection, intraperitoneal injection, intramuscular injection). For oral administration, Compound I as an acid or ester is mixed with a conventional formulation carrier, diluent, or additives and encapsulated or tabletted. It may be formulated to give a powder or granules in a conventional manner.

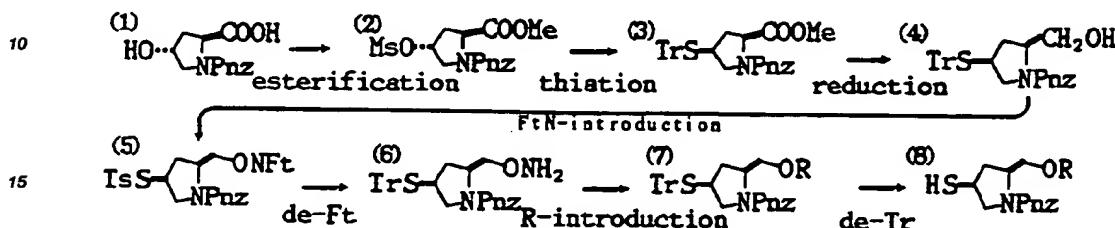
60 Preferably the daily dose is about 100 mg to 6 g (e.g., 250 mg to 3 g) for injection and about 100 mg to 6 g (e.g., 250 mg to 4 g) for oral use.

The following Examples and Experiment are given to illustrate this invention. These examples, however, are not intended to limit the scope of this invention.

The abbreviations are as follows:

Boc = t-butoxycarbonyl. Et = ethyl. Ft = phthalyl. Me = methyl. Pnz = p-nitrobenzyloxycarbonyl. Pmz = p-methoxybenzyloxycarbonyl. Tr = trityl. THF = tetrahydrofuran.

Example 1. Synthesis of 3-substituent



A. Preparation of protected thioaminooxymethylpyrrolidine

1) (2S,4R)-4-hydroxy-2-methoxycarbonyl-1-p-nitrobenzyloxycarbonylpyrrolidine (esterification)

Thionyl chloride (18.7 ml) and, after 5 minutes stirring, N-p-nitrobenzyloxycarbonyl-L-hydroxyproline (1: 72.4 g) are added dropwise to a mixture of methanol (94.5 ml) and dichloromethane (945 ml) under ice cooling and the mixture is stirred overnight at room temperature. The reaction mixture is concentrated in vacuum to give crude (2S,4R)-4-hydroxy-2-methoxycarbonyl-1-p-nitrobenzyloxycarbonylpyrrolidine (86.5 g) as pale yellow oil. This product can be used in the next step without further purification.

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3450, 1742, 1703, 1605.

<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.77(1H, s), 2.05 to 2.45(2H, m), 3.55 to 3.8(2H, m), 3.66, 3.76(3H, 2s), 4.49 to 4.62(2H, m), 5.06 to 5.35(2H, m), 7.43 to 7.56(2H, m), 8.22(2H, d,  $J$ =8.2Hz).

2) (2S,4R)-4-methanesulfonyloxy-2-methoxycarbonyl-1-p-nitrobenzyloxycarbonylpyrrolidine (2) (hydroxy activation)

Triethylamine (52 ml) and then methane-sulfonyl chloride (21.6 ml) are added to a solution of crude (2S,4R)-4-hydroxy-2-methoxycarbonyl-1-p-nitrobenzyloxycarbonylpyrrolidine (86.1 g) in dichloromethane (1 liter) under ice cooling and the mixture is stirred for 25 minutes. The reaction mixture is acidified with diluted hydrochloric acid and stirred. The organic layer is taken, washed with aqueous sodium hydrogen carbonate and water, dried over sodium sulfate, and concentrated in vacuo to give (2S,4R)-4-methanesulfonyloxy-2-methoxycarbonyl-1-p-nitrobenzyloxycarbonylpyrrolidine (2: 90.0 g) as an orange oil. This product can be used in the next step without further purification.

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 1741, 1703, 1602.

<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 2.22 to 2.82(2H, m), 3.07(3H, s), 3.67, 3.78(3H, 2s), 3.75 to 4.03(2H, m), 4.55(1H, t,  $J$ =7.8Hz), 5.08 to 5.39(3H, m), 7.43 to 7.58(2H, m), 8.23(2H, d,  $J$ =8.6Hz).

3) (2S,4S)-4-triphenylmethylthio-2-methoxycarbonyl-1-p-nitrobenzyloxycarbonylpyrrolidine (3) (thiolation)

Triphenylmethylmercaptan (10.9 g) is added in small portions to a suspension of sodium hydride (1.26 g) (60 % dispersion in oil) in dimethylformamide (50 ml) under ice cooling and stirred for 5 minutes at room temperature.

A solution of crude (2S,4R)-4-methanesulfonyloxy-2-methoxycarbonyl-1-p-nitrobenzyloxycarbonylpyrrolidine (2: 10.6 g) in dimethylformamide (80 ml) is added to this mixture, and the whole is stirred in an oil bath at 50°C overnight. The reaction mixture is diluted with ethyl acetate and mixed with ice water containing 1N-hydrochloric acid (35 ml). The organic layer is taken, washed with water and satd. brine, dried over sodium sulfate, and concentrated in vacuo. The residue is purified by silica gel chromatography (toluene-ethyl acetate) to give (2S,4S)-4-triphenylmethylthio-2-methoxycarbonyl-1-p-nitrobenzyloxycarbonylpyrrolidine (3: 9.12 g) an orange foam (Yield: 52 % from hydroxyproline) and the starting compound (2: 3.11g: Yield: 29%).

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 1745, 1702, 1602.

<sup>1</sup>HNMR δ (CDCl<sub>3</sub>) ppm: 1.64 to 2.36(2H, m), 2.68 to 3.32(2H, m), 3.32 to 3.55(1H, m), 3.61, 3.65, 3.72(3H, 3s), 4.01 to 4.27(1H, m), 4.95 to 5.32(2H, m), 7.15 to 7.53(17H, m), 8.14 to 8.27(2H, m).

5 **4) (2S,4S)-4-triphenylmethylthio-2-hydroxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (Reduction of car-**  
**bomethoxy)**

10 A solution of sodium borohydride (371 mg) in ethanol (15 ml) and a solution of lithium chloride (554 mg) in tetra-hydrofuran (15 ml) are added to a solution of (2S,4S)-4-triphenylmethylthio-2-methoxycarbonyl-1-p-nitrobenzyloxycarbonylpyrrolidine (3: 3.63 g) in tetrahydrofuran (36 ml) under ice cooling are added and the mixture is warmed to room temperature and stirred for 110 minutes. The reaction mixture is diluted with ethyl acetate under ice cooling, and neutralized with 1N-hydrochloric acid (10 ml) to decompose the remaining reagent. The organic layer is taken, washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue is purified by silica gel chromatography to give (2S,4S)-4-triphenylmethyl-thio-2-hydroxymethyl-1-p-nitro-benzyloxycarbonylpyrrolidine (4: 3.02 g) as colorless foam. Yield: 88%.

15 IR ν (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3400, 1679, 1603.  
<sup>1</sup>HNMR δ (CDCl<sub>3</sub>) ppm: 1.3 to 2.13(2H, m), 1.6(1H, brs), 2.65 to 4.3(6H, m), 5.03 to 5.2(2H, m), 7.07 to 7.55(17H, m), 8.15 to 8.3(2H, m).

20 **5) (2S,4S)-4-triphenylmethylthio-2-phthalimidoxymethyl-1-p-nitrobenzyl-oxycarbonylpyrrolidine (5) (introduction of imidoxy)**

25 Triphenylphosphine (315 mg), azodicarboxylic acid diethyl ester (189 μl), and after stirring for 5 minutes, N-hydroxy-phthalimide (196 mg) added to a solution of (2S,4S)-4-triphenylmethylthio-2-hydroxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (4: 555 mg) in tetrahydrofuran (6 ml) under ice cooling are added, and the mixture is stirred for 45 minutes. The reaction mixture is concentrated in vacuo. The residue is purified by silica gel column chromatography to give (2S,4S)-4-triphenylmethylthio-2-phthalimidoyloxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (5: 686 mg) as a pale yellow foam. Yield: 98 %.

30 IR ν (CHCl<sub>3</sub>) cm<sup>-1</sup>: 1783, 1725, 1693, 1602.  
<sup>1</sup>HNMR δ (CDCl<sub>3</sub>) ppm: 1.8 to 2.5(2H, m), 2.5 to 3.0(2H, m), 3.15 to 3.54(1H, m), 3.94(1H, brs), 4.08 to 4.5(2H, m), 4.98 to 5.25(2H, m), 7.1 to 7.6(17H, m), 7.65 to 7.95(4H, m), 8.0 to 8.3(2H, m).

35 **6) (2S,4S)-4-triphenylmethylthio-2-aminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (6) (removing phthalimido)**

40 Methylhydrazine (42 μl) is added to a solution of (2S,4S)-4-triphenylmethylthio-2-phthalimidoyloxy-methyl-1-p-nitrobenzyloxycarbonylpyrrolidine (5: 501 mg) in dichloro-methane (5 ml) at -40°C, and the mixture is stirred for 5 minutes and then under ice cooling for further 30 minutes to give a solution of (2S,4S)-4-triphenylmethylthio-2-amino-oxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (6).

45 **B. Introduction of amino substituent**

**(2S,4S)-4-triphenylmethylthio-2-acetylaminooxymethyl-1-p-nitrobenzyloxy-carbonylpyrrolidine (7a) (acetylation)**

50 Pyridine (93 μl) and acetyl chloride (66 μl) To a solution of (2S, 4S)-4-triphenylmethylthio-2-aminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (6) preparable as above A (6) in dichloromethane and the mixture is stirred for 25 minutes. 1N-hydrochloric acid (1 ml) and ethyl acetate are added to the reaction mixture. The organic layer is taken, washed with water, aqueous sodium hydrogen carbonate, and brine, dried over sodium sulfate, and concentrated in vacuo. The residue is purified by silica gel chromatography to give (2S,4S)-4-triphenylmethylthio-2-acetylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (7: 385 mg) as a pale yellow foam. Yield : 88 %.

55 In a manner similar to B above, the amino substituent is introduced to aminooxypyrrrolidine (6) produced in A(6) above under the condition given in Table 1 to give protected mercaptides. The producing condition for compounds 7a (prepared by B) to 7g is listed on Table 1.

Table 1 Reaction conditions for introducing amin substituent

	Reagent equivalents	Solv.	Base equivalents	Temp °C	Time min.	Crop %	
5	a MeCOCl	CH <sub>2</sub> Cl <sub>2</sub>	Py <sup>1)</sup>	1.6	0	25	88
	b ClCO <sub>2</sub> Me	CH <sub>2</sub> Cl <sub>2</sub>	Py	1.6	0	20	98
	c MeNCO	CH <sub>2</sub> Cl <sub>2</sub>		rt	105	100	
10	d ClSO <sub>2</sub> Me	CH <sub>2</sub> Cl <sub>2</sub>	Py	2.4	0	100	94
	e ClSO <sub>2</sub> NHCO <sub>2</sub> PMB <sup>2)</sup>	CH <sub>2</sub> Cl <sub>2</sub>	Et <sub>3</sub> N	1.2	0	30	86
	f MZ-SDP <sup>3)</sup>	C <sub>6</sub> H <sub>6</sub>		refl	100	60	
	g MeCHO	CH <sub>2</sub> Cl <sub>2</sub>		0	30	93	

15

Note: 1) pyridine. 2) prepared from chlorosulfonyl isocyanate and p-methoxybenzyl alcohol. 3) S-p-methoxybenzyloxycarbonyl-4,6-dimethyl-2-mercaptopurimidine.

20

#### Physical constants of protected mercaptide (7a to 7g)

##### Compound 7a R = acetylamino

25 IR v (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3260, 1680, 1600.

<sup>1</sup>HNMR δ (CDCl<sub>3</sub>) ppm: 1.3 to 2.37(2H, m), 1.87(3H, brs), 2.7 to 2.9(2H, m), 2.98 to 3.22(1H, m), 3.45 to 4.27(3H, m), 5.10, 5.17(2H, 2s), 7.07 to 7.54 (17H, m), 8.17 to 8.30(2H, m).

##### Compound 7b R = carbomethoxyamino

IR v (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3360, 1720, 1685, 1600.

30 <sup>1</sup>HNMR δ (CDCl<sub>3</sub>) ppm: 1.38 to 2.38(2H, m), 2.7 to 2.9(2H, m), 2.93 to 3.23(1H, m), 3.47 to 4.23(3H, m), 3.73(3H, s), 5.10, 5.17(2H, 2s), 7.1 to 7.5(17H, m), 8.13 to 8.35(2H, m).

##### Compound 7c R = methylcarbamoylamino

IR v (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3445, 3310, 1685, 1602.

35 <sup>1</sup>HNMR δ (CDCl<sub>3</sub>) ppm: 1.3 to 2.3(2H, m), 2.7 to 2.92(2H, m), 2.8(3H, brs), 3.05 to 3.58(1H, m), 3.5 to 4.2(3H, m), 5.0 to 5.25(2H, m), 6.12 (1H, brs), 7.1 to 7.52(17H, m), 8.15 to 8.3(2H, m).

##### Compound 7d R = mesylamino

IR v (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3260, 1687, 1602.

40 <sup>1</sup>HNMR δ (CDCl<sub>3</sub>) ppm: 1.2 to 2.35(2H, m), 2.65 to 2.9(2H, m), 2.96(3H, s), 2.95 to 3.6(1H, m), 3.73 to 4.35(3H, m), 5.08, 5.16(2H, 2s), 7.05 to 7.55(17H, m), 7.86, 7.95(1H, 2s), 8.1 to 8.3(2H, m).

##### Compound 7e' R = N-sulfamoyl-N-Pbz-amino

IR v (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3370, 3245, 1727, 1687, 1601.

45 <sup>1</sup>HNMR δ (CDCl<sub>3</sub>) ppm: 1.35 to 2.35(2H, m), 2.65 to 3.6(3H, m), 3.76(3H, s), 3.8 to 4.25(3H, m), 4.95 to 5.2(3H, m), 6.75 to 6.9(2H, m), 7.08 to 7.55(19H , m), 7.6 to 8.4(3H, m).

##### Compound 7f' R = Pbz-amino

45 IR v (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3375, 1740, 1695, 1607.

<sup>1</sup>HNMR δ (CDCl<sub>3</sub>) ppm: 1.35 to 2.33(2H, m), 2.65 to 3.6(3H, m), 3.79(3H, s), 3.65 to 4.2(3H, m), 4.95 to 5.25(4H, m), 6.87(2H, d, J=9Hz), 7.07 to 7.55(19H, m), 8.1 to 8.3(3H, m).

##### Compound 7g R = ethyldeneamino

IR v (CHCl<sub>3</sub>) cm<sup>-1</sup>: 1692, 1600.

50 <sup>1</sup>HNMR δ (CDCl<sub>3</sub>) ppm: 1.65 to 2.3(2H, m), 1.75 to 1.85(3H, m), 2.6 to 3.62(3H, m), 3.78 to 4.35(3H, m), 5.0 to 5.25(2H, m), 6.71(0.5H, q, J=5.6Hz), 7.1 to 7.6 (17.5H, m), 8.1 to 8.3(2H, m).

#### C. Modification of protected amino

55 1) (2S,4S)-4-triphenylmethylthio-2-sulfamoylaminoxyethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (7e)  
(deprotection at aminoxy)

Anisol (10 ml) and trifluoroacetic acid (10 ml) are added to a solution of (2S,4S)-4-triphenylmethylthio-2-

N-p-methoxybenzyloxycarbonylsulfamoylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidin (7': 9.2 g) in dichloromethane (100 ml) under ice cooling, and the mixture is stirred for 1 hour and concentrated in vacuo. The residue is purified by silica gel chromatography to give (2S,4S)-4-triphenylmethylthio-2-sulfamoylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (7e: 5.74 g) as a yellow foam. Yield: 78 %.

5 Compound 7e R = sulfamoylamino

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3440, 3355, 3245, 1692, 1607.

<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.3 to 2.4(2H, m), 2.7 to 3.6(3H, m), 3.75 to 4.3 (3H, m), 4.9 to 5.25(3H, m), 7.08 to 7.6(17H, m), 7.6 to 7.75(1H, m), 8.1 to 8.3(2H, m).

10 2) (2S,4S)-4-triphenylmethylthio-2-N-p-methoxybenzyloxycarbonyl-N-methylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (7f') (methylation at aminoxy)

15 A solution of (2S,4S)-4-triphenylmethylthio-2-N-p-methoxybenzyloxycarbonylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (7f: 965 mg) in dimethylformamide (2 ml) and, after stirring for 15 minutes, methyl iodide (164  $\mu$ l), are added dropwise to a suspension of sodium hydride (57.9 mg: 60 % dispersion in oil) in dimethylformamide (8 ml) under ice cooling are dropwise and the mixture is stirred for 30 minutes. The reaction mixture is diluted with ethyl acetate, washed with water, dried over sodium sulfate, and concentrated in vacuo to give crude (2S,4S)-4-tri-phenylmethylthio-2-N-p-methoxybenzyloxycarbonyl-N-methylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (7f': 821 mg). This product can be used in the next step without further purification.

20 Compound 7f' R = N-methyl-N-Prmz-amino

<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.7 to 2.3(2H, m), 2.6 to 3.65(3H, m), 3.08(3H, s), 3.7 to 4.2(3H, m), 3.76, 3.78(3H, 2s), 4.95 to 5.25(4H, m), 6.8 to 7.0(2H, m), 7.1 to 7.6(19H, m), 8.05 to 8.35(2H, m).

25 3) (2S,4S)-4-triphenylmethylthio-2-methylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (7f) (deprotection at aminoxy)

30 Anisole (1 ml) and trifluoroacetic acid (1 ml) are added to a solution of crude (2S,4S)-4-triphenylmethylthio-2-N-p-methoxybenzyloxycarbonyl-N-methylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (7f': 821 mg) in dichloromethane (8.2 ml) under ice cooling and the mixture is stirred for 20 minutes and concentrated in vacuo. The residue is purified by silica gel chromatography to give (2S,4S)-4-tri-phenylmethylthio-2-N-methylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (7f) trifluoroacetate (843 mg). Yield: 94 %.

Compound 7f R = methylamino

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3400, 1685, 1605.

35 <sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.47 to 2.42(2H, m), 2.65 to 3.52(3H, m), 2.84(3H, s), 4.02 to 4.45(3H, m), 5.09, 5.15(2H, 2s), 7.1 to 7.6(17H, m), 8.05 to 8.5(2H, m).

#### D. Deprotection at thiol

40 (2S,4S)-4-mercaptop-2-acetylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (8a) (detritylation)

45 Pyridine (149  $\mu$ l) and then a solution of silver nitrate (289 mg) in a mixture of water (1.5 ml) and methanol (15ml) are added dropwise to a solution of (2S,4S)-4-tritylthio-2-acetylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidine (7a: 452 mg) in methanol (9 ml) under ice cooling, and the mixture is stirred for 25 minutes. Separating silver salt is collected by filtration, washed with methanol, ether, and petroleum ether, and dried. Hydrogen sulfide gas is introduced to a suspension of this crude silver salt in a mixture of dichloromethane (3.5 ml) and methanol (3.5 ml) for 5 minutes. The resulting silver sulfide is filtered off and washed with a mixture of methanol and dichloromethane. The filtrate is concentrated in vacuo. The residue is purified by silica gel chromatography to give (2S,4S)-4-mercaptop-2-acetylaminoxy-methyl-1-p-nitrobenzyloxycarbonylpyrrolidine (8a: 198 mg) as a pale yellow foam. Yield: 73 %.

50 Under the reaction condition listed in Table 2, the protected mercaptide (7a to 7g) is deprotected to give mercaptopyrrolidine (8a to 8g) in a handling similar to the above.

Table 2 Removing of mercapto protective group

5	amino substituent in R	Solvent	pyridine equiv.	AgNO <sub>3</sub> equiv.	Crop (%)
	a acetyl	MeOH	2.5	2.3	73
10	b methoxycarbonyl	MeOH	2.5	2.3	64
	c methylcarbamoyl	MeOH	2.5	2.3	73
	d mesyl	MeOH-THF	2.5	2.3	68
	e sulfamoyl	MeOH-THF	2.5	2.3	62
15	f methyl	MeOH	3.5	2.3	50
	g ethylidene	MeOH-THF	2.5	2.3	72

## Physical constants of mercaptopyrrolidine (8a to 8g)

20 Compound 8a R = acetylamino  
IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3350, 1687, 1603.  
<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>-CD<sub>3</sub>OD) ppm: 1.65 to 2.15(1H, m), 1.89(3H, s), 2.52 to 2.72(1H, m), 3.1 to 3.45(2H, m), 3.95 to 4.3(4H, m), 5.23(2H, m), 7.53(2H, d, J=8.8Hz), 8.24(2H, d, J=8.8Hz).

Compound 8b R = carbomethoxyamino  
25 IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3360, 1742, 1690, 1601.  
<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.5 to 1.82(2H, m), 1.78(1H, d, J=6.6Hz), 2.5 to 2.7(1H, m), 3.06 to 3.44(2H, m), 3.76(3H, s), 3.88 to 4.4(4H, m), 5.23(2H, s) 7.52(2H, d, J=8.8Hz), 8.23(2H, d, J=8.8Hz).

Compound 8c R = methylcarbamoylamino  
30 IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3440, 3325, 1683, 1602.  
<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.4 to 1.9(2H, m), 1.78(1H, d, J=6.4Hz), 2.51 to 2.69(1H, m), 2.83(3H, d, J=4.8Hz), 3.1 to 3.47(2H, m), 3.88 to 4.4(4H, m), 5.23(2H, s), 7.52(2H, d, J=8.8Hz), 8.23(2H, d, J=8.8Hz).

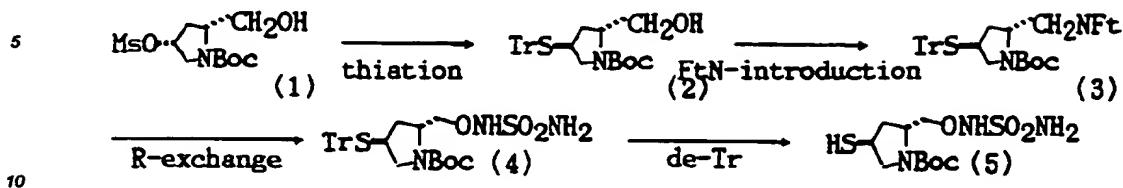
Compound 8d R = mesylamino  
35 IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3270, 1692, 1600.  
<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.45 to 1.65(1H, m), 1.79(1H, d, J=6.2Hz), 2.5 to 2.7(1H, m), 3.01(3H, s), 3.03 to 3.5(2H, m), 3.97 to 4.5(4H, m), 5.22(2H, s), 7.52(2H, d, J=8.8Hz), 7.92(1H, s), 8.23(2H, d, J=8.8Hz).

Compound 8e R = sulfamoylamino  
40 IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3375, 3320, 3220, 1679, 1595.  
<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.45 to 1.75(1H, m), 1.81(1H, d, J=6.4Hz), 2.5 to 2.7(1H, m), 3.1 to 3.5(2H, m), 4.0 to 4.45(4H, m), 5.21(2H, s), 5.29(2H, s), 7.52(2H, d, J=8.6Hz), 7.77(1H, s), 8.22(2H, d, J=8.6Hz).

Compound 8f R = methylamino  
45 IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3370, 1698, 1602.  
<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.65 to 2.05(2H, m), 1.84(3H, d, J=5.8Hz), 2.45 to 2.65(1H, m), 3.0 to 3.4(2H, m), 3.97 to 4.5(4H, m), 5.23(2H, s), 6.75(0.5H, q, J=5.8Hz), 7.42(0.5H, q, J=5.8Hz), 7.53(2H, d, J=9.0Hz), 8.22(2H, d, J=9.0Hz).

50

55

E. Preparation of stereoisomeric aminoxyethylpyrrolidine1) (2R,4S)-1-t-butoxycarbonyl-4-tritylthiopyrrolidine-2-methanol (2) (thiation)

15      A solution of tritylmercaptane (1.41 g: 5.09 mMol.) and sodium hydride (178 mg: 4.41 mMol.) in tetrahydrofuran (8.8 ml) are added dropwise to a solution of (2R,4S)-1-t-butoxycarbonyl-4-mesyloxy-2-methanol (1: 1.00 g: 3.34 mMol.) in tetrahydrofuran (3.4 ml) at room temperature and the mixture is stirred at room temperature for 100 minutes. The reaction mixture is diluted with ethyl acetate (30 ml) and ice water (30 ml). The organic layer is taken, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel chromatography to give (2R,4S)-1-t-butoxycarbonyl-4-tritylthiopyrrolidine-2-methanol (2: 1.42 g). Yield : 88 %.

20      IR  $\nu$  (KBr)  $\text{cm}^{-1}$ : 3430, 1690.

25       $^1\text{H}$ NMR  $\delta$  ( $\text{CDCl}_3$ ) ppm: 1.2 to 1.5 (m, 1H), 1.43 (d,  $J=1.6\text{Hz}$ , 9H), 1.6 to 1.9 (m, 1H), 2.7 to 3.5 (m, 5H), 3.8 to 4.0 (m, 1H), 7.1 to 7.6 (m, 15H).

2) (2R,4S)-1-t-butoxycarbonyl-2-phtalimidooxymethyl-4-tritylthiopyrrolidine (3) (introduction of imidoxy)

30      Triphenylphosphin (892 mg: 3.40 mMol.), N-hydroxy-phthalimide (705 mg: 4.32 mMol.) and azodicarboxylic acid diethyl ester (0.59 ml: 3.74 mMol) are added to a solution of (2R,4S)-1-t-butoxycarbonyl-4-tritylthiopyrrolidine-2-methanol (2: 1.37 g: 2.88 mMol.) in tetrahydrofuran (8.6 ml) under ice cooling and the mixture is stirred under ice cooling for 90 minutes. The reaction mixture is diluted with ethyl acetate (30 ml) and ice water (30 ml). The organic layer is taken, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel chromatography to give (2R,4S)-1-t-butoxycarbonyl-2-phtalimidooxymethyl-4-tritylthiopyrrolidine (3: 1.73 g). Yield : 97 %.

35      IR  $\nu$  (KBr)  $\text{cm}^{-1}$ : 3420, 1790, 1735, 1694.

40       $^1\text{H}$ NMR  $\delta$  ( $\text{CDCl}_3$ ) ppm: 1.35 (s, 9H), 1.8 to 2.4 (m, 2H), 2.7 to 3.2 (m, 2H), 3.8 to 4.3 (m, 2H), 7.1 to 7.6 (m, 15H), 7.6 to 7.9 (m, 4H).

3) (2R,4S)-1-t-butoxycarbonyl-2-sulfamidoxyethyl-4-tritylthiopyrrolidine (4) (modification at aminoxy)

45      Methylhydrazine 187  $\mu\text{l}$  (3.54 mMol) at -30°C is added dropwise to a solution of (2R,4S)-1-t-butoxycarbonyl-2-phtalimidooxymethyl-4-tritylthiopyrrolidine (3: 2.00 g: 3.22 mMol.) in dichloromethane (25.8 ml) in nitrogen, and the mixture is stirred at the same temperature for 35 minutes and under ice cooling for 25 minutes. The reaction mixture is diluted with dichloromethane (25 ml) and the separating crystals are removed by filtration. The filtrate is washed with saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure.

50      A solution of triethylamine (895  $\mu\text{l}$ : 6.44 mMol) and sulfamoyl chloride (4.83 mMol) in dichloromethane is added to a solution of the residue in dichloromethane (25.0 ml) at -40°C and the mixture is stirred at -40°C for 40 minutes, and then diluted with water (30 ml). The organic layer is taken, washed with aqueous sodium hydrogen carbonate and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel chromatography to give (2R,4S)-1-t-butoxycarbonyl-2-sulfamidoxyethyl-4-tritylthiopyrrolidine (4: 1.45 g). Yield : 81 %.

55      IR  $\nu$  (KBr)  $\text{cm}^{-1}$ : 3400, 3240, 1670.

55       $^1\text{H}$ NMR  $\delta$  ( $\text{CDCl}_3$ ) ppm: 1.1 to 1.4 (m, 1H), 1.41 (s, 9H), 1.6 to 1.9 (m, 1H), 2.7 to 3.2 (m, 3H), 3.2 to 3.9 (m, 2H), 3.9 to 4.3 (m, 1H), 4.6 to 5.1 (m, 2H), 7.1 to 7.6 (m, 15H), 7.8 to 8.0 (m, 1H).

4) (2R,4S)-1-t-butoxycarbonyl-2-sulfamidoxyethyl-4-mercaptopyrrolidine (5) (Deprotection at thiol)

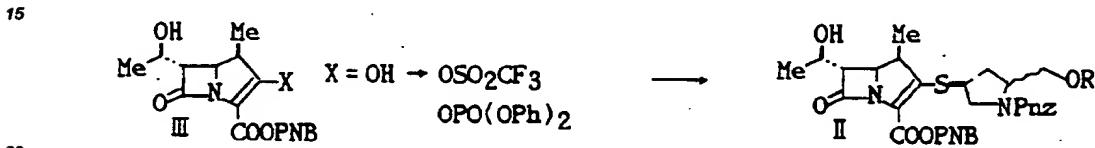
55      A solution of pyridin (0.49 ml: 6.05 mMol.), silver nitrate (945 mg: 5.57 mMol.) in water (4.7 ml) - m thanol

(47.0 ml) is added to a solution of (2R,4S)-1-t-butoxycarbonyl-2-sulfamidooxymethyl-4-tritylthiopyrrolidine (4: 1.35 g; 2.42 mMol.) in a mixture of methanol (24.3 ml) and tetrahydrofuran (2.7 ml) under ice cooling, and the mixture is stirred at the same temperature for 40 minutes, and concentrated under reduced pressure. The residue is washed with toluene and again concentrated under reduced pressure. Hydrogen sulfide is bubbled through a solution of the residue in dichloromethane (24.2 ml) - methanol (7.3 ml) under ice cooling for 5 minutes. The reaction mixture is diluted with dichloro-methane (30 ml), filtered to remove black precipitate, and the filtrate is concentrated under reduced pressure. The residue is purified by silica gel chromatography to give (2R,4S)-1-t-butoxycarbonyl-2-sulfamidooxymethyl-4-mercaptopyrrolidine (5: 502 mg). Yield: 64 %.

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3440, 3350, 3280, 1682.

<sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.47(s, 9H), 1.6 to 1.8(m, 3H), 1.8 to 2.2(m, 1H), 3.2 to 3.5(m, 2H), 3.6 to 4.1(m, 3H), 4.2 to 4.5(m, 1H), 5.10(s, 2H), 7.8 to 8.0 (m, 1H).

Example 2. Condensation



1) (1R,5S,6S)-2-[(3S,5S)-(5-acetylaminooxymethyl-1-p-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-nitrobenzyl ester (IIa)

25 Diisopropylethylamine (89  $\mu$ l) and trifluoromethanesulfonic acid anhydride (71  $\mu$ l) are added to a solution of (1R,5S,6S)-2-oxo-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-nitrobenzyl ester (154 mg) in acetonitrile (3 ml) at -40°C and the mixture is stirred for 15 minutes to give a solution of (1R,5S,6S)-2-trifluoromethanesulfonyloxy-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-nitrobenzyl ester (III).

30 A solution of diisopropylethylamine (89  $\mu$ l) and 4-mercaptop-2-acetylaminooxymethyl-1-p-nitrobenzyloxy-carbonylpyrrolidine (8a: 190 mg) in acetonitrile (1.5 ml) is added dropwise to this solution of (III) at -40°C and the mixture is stirred at the same temperature for 2 hours and under ice cooling for 30 minutes and diluted with ethyl acetate. The reaction mixture is washed with water and saturated brine, dried over sodium sulfate, and concentrated in vacuo. The residue is purified by silica gel chromatography to give (1R,5S,6S)-2-[(3S,5S)-5-acetylaminooxymethyl-1-p-nitrobenzyloxycarbonylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid p-nitrobenzyl ester (IIa: 270 mg) as a pale yellow powder. Yield: 89 %.

35 Under the conditions listed in Table 3, trifluoromethanesulfonate (III) is condensed with mercaptopyrrolidine (8a to 8g) by a manner similar to the one for the corresponding carbapenem (IIa to IIg).

40 Table 3 Reaction conditions of condensation

45	Product carbapenem II amino substituent in R	Starting thiol equivalents	Time (min.) at -40°C and 0°C	Crop (%)
a acetyl	8 a (1.2)	120	30	89
b carbomethoxy	8 b (1.2)	30	30	78
c methylcarbamoyl	8 c (1.2)	45	40	83
50 d mesyl	8 d (1.2)	65	--	82
e sulfamoyl	8 e (1.2)	70	35	72
f methyl	8 f (1.2)	30	30	63
g ethylidene	8 g (1.2)	25	65	74

55 Physical constants of protected carbapenems (II)

Compound IIa R = acetylamino

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3365, 1765, 1690, 1602.

<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.28(3H, d, J=7.2Hz), 1.37(3H, d, J=6.2Hz), 1.4 t 2.2(3H, m), 1.91(3H, s), 2.52 to 2.7(1H, m), 3.28(1H, dd, J<sub>1</sub>=6.2Hz, J<sub>2</sub>=2.6Hz), 3.22 to 3.45(2H, m), 3.55 to 4.48(7H, m), 5.23, 5.50(2H, ABq, J= 13.7Hz), 5.24(2H, s), 7.52(2H, d, J=8.8Hz), 7.65(2H, d, J=8.8Hz), 8.22 (2H, d, J=8.8Hz), 8.23(2H, d, J=8.8Hz).

5 Compound IIb R = carbomethoxyamino

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3375, 1765, 1695, 1602.

<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.28 (3H, d, J=7.2Hz), 1.37 (3H, d, J=6.2Hz), 1.64 (2H, brs), 1.7 to 1.9(1H, m), 2.48 to 2.72(1H, m), 3.28(1H, dd, J<sub>1</sub>=6.2 Hz, J<sub>2</sub>=2.6Hz), 3.22 to 3.43(2H, m), 3.58 to 3.82(1H, m), 3.76(3H, s), 3.9 to 4.45(6H, m), 5.23, 5.50(2H, ABq, J=13.7Hz), 5.23(2H, s), 7.52 (2H, d, J=8.8Hz), 7.65(2H, d, J=8.8Hz), 8.23(2H, d, J=8.8Hz), 8.24(2H, d, J= 8.8Hz).

10 Compound IIc R = methylcarbamoylamino

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3440, 3380, 3330, 1767, 1685, 1601.

<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.26(3H, d, J=7.4Hz), 1.37 (3H, d, J=6.2Hz), 1.73 (3H, brs), 2.42 to 2.75(1H, m), 2.83(3H, d, J=4.8Hz), 3.2 to 3.45(2H, m), 3.28(1H, dd, J<sub>1</sub>=6.2Hz, J<sub>2</sub>=2.6Hz), 3.58 to 4.47(7H, m), 5.22, 5.51 (2H, ABq, J=13.0Hz), 5.23(2H, s), 7.52(2H, d, J=8.8Hz), 7.65(2H, d, J= 8.8Hz), 8.22(2H, d, J=8.8Hz), 8.23(4H, d, J=8.8Hz).

15 Compound IId R = mesylamino

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3410, 3280, 3190, 1768, 1698, 1602.

20 <sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.29(3H, d, J=7.2Hz), 1.37(3H, d, J=6.8Hz), 1.73 to 2.13 (1H, m), 1.98(2H, s), 2.54 to 2.78(1H, m), 3.03(3H, s), 3.29(1H, dd, J<sub>1</sub>=6.8Hz, J<sub>2</sub>=2.6Hz), 3.2 to 3.5(2H, m), 3.62 to 4.5(7H, m), 5.22(2H, s), 5.22, 5.50 (2H, ABq, J=13.6Hz), 7.43 to 7.66 (2H, m), 7.65 (2H, d, J= 8.8Hz), 8.22(2H, d, J=8.8Hz), 8.24(2H, d, J=8.8Hz).

25 Compound IIe R = sulfamoylamino

IR  $\nu$  (KBr) cm<sup>-1</sup>: 3390, 3235, 3105, 3080, 1762, 1696, 1602.

<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>-CD<sub>3</sub>OD) ppm: 1.27(3H, d, J=7.2Hz), 1.34(3H, d, J=6.2Hz), 1.77 to 2.2(1H, m), 2.35 to 2.78(1H, m), 3.27(1H, dd, J<sub>1</sub>=6.2Hz, J<sub>2</sub>=2.6 Hz), 3.3 to 3.46(2H, m), 3.63 to 3.82(1H, m), 3.97 to 4.4(6H, m), 5.22 (2H, s), 5.24, 5.48(2H, ABq, J=13.7Hz), 7.47 to 7.62(2H, m), 7.66(2H, d, J=8.8Hz), 8.22(2H, d, J=8.8Hz), 8.23(2H, d, J=8.8Hz).

30 Compound IIIf R = methylamino

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3390, 1767, 1697, 1602.

<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.28 (3H, d, J=7.8Hz), 1.37 (3H, d, J=6.8Hz), 1.75 to 2.15 (1H, m), 2.38 to 2.7(1H, m), 2.68(3H, s), 3.15 to 3.53(2H, m), 3.27(1H, dd, J<sub>1</sub>=6.8Hz, J<sub>2</sub>=2.6Hz), 3.5 to 4.35(7H, m), 5.23(2H, s), 5.23, 5.51(2H, ABq, J= 13.2Hz), 7.53(2H, d, J=8.8Hz), 7.65(2H, d, J=8.8Hz), 8.22(4H, d, J=8.8Hz).

35 Compound IIg R = ethylenediamino

IR  $\nu$  (CHCl<sub>3</sub>) cm<sup>-1</sup>: 3370, 1768, 1700, 1603.

<sup>1</sup>HNMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.28(3H, d, J=7.0Hz), 1.37(3H, d, J=6.4Hz), 1.65(1H, brs), 1.82(3/2H, d, J=5.6Hz), 1.83(3/2H, d, J=5.6Hz), 1.9 to 2.2(1/2H, m), 2.4 to 2.65(1/2H, m), 3.15 to 3.75(4H, m), 3.9 to 4.4(7H, m), 5.25(2H, s), 5.24, 5.52(2H, ABq, J=14Hz), 6.75(1/2H, q, J=5.6Hz), 7.40(1/2H, q, J=5.6Hz), 7.54(2H, d, J=8.8Hz), 7.66(2H, d, J=8.8Hz), 8.23(2H, d, J=8.8Hz).

2) (1R,5S,6S)-2-[(3S,5R)-1-t-butoxycarbonyl-5-sulfamidooxymethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid diphenylmethyl ester

45 A solution of diisopropylethylamine (0.30 ml: 1.73 mMol.) in acetonitrile (2.1 ml) is added dropwise to a solution of (1R,5S,6S)-2-diphenoxypyrophosphonyloxy-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid diphenylmethyl ester (832 mg: 1.33 mMol.) and (2R,4S)-1-t-butoxycarbonyl-2-sulfamido-oxymethyl-4-mercaptopyrrolidine (522 mg: 1.59 mMol.) in acetonitrile (4.2 ml) in nitrogen under ice cooling, and the mixture is stirred at the same temperature for 3 hours. The mixture is diluted with ethyl acetate (30 ml) and ice water (30 ml). The organic layer is taken, washed with water and saturated brine, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is purified by silica gel chromatography to give (1R,5S,6S)-2-[(3S,5R)-1-t-butoxycarbonyl-5-sulfamidooxymethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid diphenylmethyl ester (843 mg). Yield : 90 %.

IR  $\nu$  (KBr) cm<sup>-1</sup>: 3390, 3240, 1765.

55 <sup>1</sup>NMR  $\delta$  (CDCl<sub>3</sub>) ppm: 1.26(d, J=7.2Hz, 3H), 1.42(s, 9H), 3.1 to 3.5(m, 2H), 3.52~4.4(m, 5H), 5.22 to 5.4(m, 1H), 5.6 to 5.8(m, 1H), 6.93(s, 1H), 7.1 to 7.7(m, 10H), 7.7 to 7.9(m, 1H). UV  $\lambda$  max : 321 nm.

IR  $\nu$  (KBr)  $\text{cm}^{-1}$ : 3300, 3210, 1749, 1588.

UV  $\lambda_{\text{max}}$   $\epsilon$  ( $\text{H}_2\text{O}$ ) nm: 297 (9400).

$^1\text{H}$ NMR  $\delta$  ( $\text{D}_2\text{O}$ ) ppm: 1.21(3H, d,  $J=7.4\text{Hz}$ ), 1.28(3H, d,  $J=6.2\text{Hz}$ ), 1.6 to 1.78(1H, m), 2.58 to 2.77(1H, m), 3.25 to 3.46(2H, m), 3.45(1H, dd,  $J_1=6.2\text{Hz}$ ,  $J_2=2.6\text{Hz}$ ), 3.53 to 3.65(1H, m), 3.89 to 4.1(2H, m), 4.13 to 4.35(4H, m).

5

m).

Elemental Analysis      Calcd.: C, 40.43; H, 5.66; N, 12.58; S, 14.39.

10      ( $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2 \cdot 0.5\text{H}_2\text{O}$ )      Found : C, 40.23; H, 5.88; N, 12.58; S, 14.30.

15      This compound shows potent antibacterial activity in vitro against e.g., *Escherichia coli* SR5028 (0.05  $\mu\text{g}/\text{ml}$ ) and *Pseudomonas aeruginosa* A25619 (0.1  $\mu\text{g}/\text{ml}$ ) and SR1012 (0.4  $\mu\text{g}/\text{ml}$ ); potent prevention of infection in mice caused by e.g., *Staphylococcus aureus* Smith (0.038 mg/kg) and *Pseudomonas aeruginosa* SR24 (0.20 mg/kg); and a high urinay recovery in mice (45 %).

Compound If R = methylamino

IR  $\nu$  (KBr)  $\text{cm}^{-1}$ : 3400, 3260, 1751, 1592.

UV  $\lambda_{\text{max}}$   $\epsilon$  ( $\text{H}_2\text{O}$ ) nm: 297 (9000).

20       $^1\text{H}$ NMR  $\delta$  ( $\text{D}_2\text{O}$ ) ppm: 1.21(3H, d,  $J=7.4\text{Hz}$ ), 1.28(3H, d,  $J=6.2\text{Hz}$ ), 1.64 to 1.83(1H, m), 2.67(3H, s), 2.6 to 2.8(1H, m), 3.29 to 3.45(2H, m), 3.46(1H, dd,  $J_1=6.2\text{Hz}$ ,  $J_2=2.6\text{Hz}$ ), 3.58 to 3.72(1H, m), 3.9 to 4.08(4H, m), 4.17 to 4.33(2H, m).

This compound shows potent antibacterial activity in vitro against e.g., *Escherichia coli* H (0.05  $\mu\text{g}/\text{ml}$ ) and a high urinay recovery in mice (52.1 %).

25      Compound Ig R = ethylideneamino ( $E : Z = 1 : 1$ )

IR  $\nu$  (KBr)  $\text{cm}^{-1}$ : 3420, 1757, 1590.

UV  $\lambda_{\text{max}}$   $\epsilon$  ( $\text{H}_2\text{O}$ ) nm: 297(9300).

25       $^1\text{H}$ NMR  $\delta$  ( $\text{D}_2\text{O}$ ) ppm: 1.22(3H, d,  $J=7.2\text{Hz}$ ), 1.28(3H, d,  $J=6.2\text{Hz}$ ), 1.7 to 1.9(1H, m), 1.86, 1.89(3H, 2d,  $J_1=6.0\text{Hz}$ ,  $J_2=5.6\text{Hz}$ ), 2.62 to 2.82(1H, m), 3.26 to 3.47(2H, m), 3.44 to 3.52(1H, m), 3.57 to 3.75(1H, m), 3.92 to 4.17(2H, m), 4.15 to 4.48(4H, m), 7.0, 7.62(1H, 2q,  $J_1=5.6\text{Hz}$ ,  $J_2=6.0\text{Hz}$ ).

30      This compound shows potent antibacterial activity in vitro against e.g., *Pseudomonas aeruginosa* PAO1-Jdg (0.02  $\mu\text{g}/\text{ml}$ ); high maximum blood level in mice (27.7  $\mu\text{g}/\text{ml}$ ); and a high urinay recovery in mice (39.4 %).

## 2) Deprotection to afford (3S,5R)-mercaptopyrrolidine isomer

35      A solution of aluminum chloride (1.22 g: 9.12 mMol.) in a mixture of dichloromethane (9.1 ml) - anisole (9.1 ml) - nitromethane (9.1 ml) is added dropwise to a solution of (1R,5S,6S)-2-[(3S,5R)-1-t-butoxycarbonyl 5-sulfamidooxymethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid diphenylmethyl ester (800 mg: 1.14mMol.) in dichloromethane (4.6 ml) at -35°C and the mixture is stirred at the same temperature for 3 hours. The reaction mixture is diluted a solution of sodium acetate (2.25 g) in water (23 ml). The aqueous layer is taken, washed with dichloromethane and purified by column chromatography over styrene-divinylbenzene copolymer to give (1R, 5S,6S)-2-[(3S,5R)-5-sulfamidooxymethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (364 mg). Yield : 73 %.

IR  $\nu$  (KBr)  $\text{cm}^{-1}$ : 3400, 1750.

45       $^1\text{H}$ NMR  $\delta$  ( $\text{D}_2\text{O}$ ) ppm: 1.18(d,  $J=7.0\text{Hz}$ , 3H), 1.24(d,  $J=6.4\text{Hz}$ , 3H), 2.12 to 2.4(m, 2H), 3.22 to 3.5(m, 3H), 3.68(dd,  $J=5.4\text{Hz}$ ,  $J=12.4\text{Hz}$ , 1H), 4.0 to 4.4(m, 6H).

UV  $\lambda_{\text{max}}$  : 296nm.

50      This compound shows potent antibacterial activity in vitro against e.g., *Morgaia morganii* SR9 (0.2  $\mu\text{g}/\text{ml}$ ) and *Pseudomonas aeruginosa* A25619 (0.1  $\mu\text{g}/\text{ml}$ ), and *Pseudomonas aeruginosa* SR1012 (0.4  $\mu\text{g}/\text{ml}$ ).

## Example 4. Modification at the pyrrolidine nitrogen



(1R,5S,6S)-2-[(3S,5S)-1-iminomethyl-5-methanesulfonylaminoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (Ih)

5 1N-sodium hydroxide and ethylformimidate hydrochloride (270 mg) are added to a solution of (1R,5S,6S)-2-[(3S,5S)-5-methanesulfonylaminoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (Id: 62 mg) in a phosphate buffer (15 ml) of pH 7.1 under ice cooling in several portions while keeping the reaction medium at pH 8.5, and the mixture is stirred at the same temperature for 25 minutes. The reaction mixture is adjusted to pH 7.0 with 1N-hydrochloric acid, purified by chromatography on styrene-divinylbenzene copolymer, and lyophilized to give (1R,5S,6S)-2-[(3S,5S)-5-methanesulfonylaminoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (Ih: 49 mg) as colorless foam.

10 Yield: 63 %.

15 Compound Ih R<sup>3</sup> = iminomethyl, R = amino

IR v (KBr) cm<sup>-1</sup>: 3360, 1748, 1701, 1630, 1582.

UV  $\lambda_{\text{max}}$  ε (H<sub>2</sub>O) nm: 297 (8700).

20 <sup>1</sup>H NMR δ (D<sub>2</sub>O) ppm: 1.21(3H, d, J=7.4Hz), 1.29(3H, d, J=6.2Hz), 1.8 to 2.03 (1H, m), 2.6 to 2.85(1H, m), 3.14(3H, s), 3.3 to 3.6(2H, m), 3.46 (1H, dd, J<sub>1</sub>=6.2Hz, J<sub>2</sub>=2.8Hz), 3.88 to 4.52(7H, m), 8.08(1H, s).

Example 5. Stereoisomers at position 5 of pyrrolidinylthio

25 In a manner similar to those of Examples 1 to 4, the stereoisomers (1R,5S,6S)-2-[(3R,5S)-5-acetamidoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid, (1R,5S,6S)-2-[(3R,5R)-5-methylcarbamoylaminoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid, (1R,5S,6S)-2-[(3R,5S)-5-sulfamoylaminoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid, (1R,5S,6S)-2-[(3R,5R)-5-sulfamoylaminoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid, (1R,5S,6S)-2-[(3R,5S)-5-methanesulfonylaminoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid, and (1R,5S,6S)-2-[(3R,5R)-5-methanesulfonylaminoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid are prepared from the stereoisomers at position 4 of (D or L)-hydroxyproline.

Formulation Example 1. (injection)

35 The sodium salt of (1R,5S,6S)-2-[(3S,5S)-5-methanesulfonylaminoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (1 g) in a 5 ml vial may be dissolved in sterilized water for injection (1 ml) before use and given by intravenous injection thrice a day to an adult patient suffering from pyelitis.

Formulation Example 2. (infusion)

40 An aqueous solution of sodium (1R,5S,6S)-2-[(3S,5S)-5-sulfamidoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylate (1 g) may be adjusted to pH 7.5 with sodium hydrogen carbonate is placed in a 150 ml bottle and lyophilized. The lyophilizate is dissolved in sterilized water for injection (100 ml) and may be dripped intravenously to an adult patient immediately after or during a surgical operation for preventing post operative bacterial infection.

Formulation Example 3. (suspension)

45 Microcrystalline (1R,5S,6S)-2-[(3S,5R)-5-sulfamidoxyethylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (2 g) in a 5 ml vial is suspended in sterilized water (3 ml) for injection, and may be given intramuscularly twice a day to an adult patient suffering from suppurative inflammation.

Experiment. Stability against human renal dehydropeptidase-1

50 A solution (1 μl) of test carbapenem compound (50 μg) in 50 mM-tris-hydrochloric acid buffer (pH 7.5: 1 ml) is added to a solution of human renal dehydropeptidase-1 in 50mM tris-hydrochloric acid buffer (pH 7.5: 0.33 unit/ml: 10 μl), and the mixture is stirred at 37°C for 60 minutes. The reaction is quenched with methanol

(10  $\mu$ l) and diluted with 0.1M phosphate buffer (pH 7.0: 80  $\mu$ l). The remaining anti-bacterial potency of this solution is measured.

Among compounds of formula I, I<sub>d</sub> (R = methan sulfonylamino) showed 71 % and I<sub>e</sub> (R = sulfamoylamino) showed 78 % activity.

5 In contrast, known compounds, (5R,6S)-2-formimidoylaminoethylthio-6-[(1R)-1-hydroxyethyl]-1-carba-2-penem-3-carboxylic acid (imipenem), (5R,6S)-2-[1-(1-acetoimidoyl)pyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]carba-2-penem-3-carboxylic acid (CS533) and (1R,5S,6S)-2-[(3S,5S)-5-dimethylaminocarbonylpyrrolidin-3-ylthio]-6-[(1R)-1-hydroxyethyl]-1-methyl-1-carba-2-penem-3-carboxylic acid (Meropenem) showed values of 51%, 48%, and 69%, respectively.

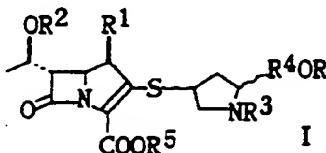
10

### Claims

1. An aminoxyppyrrolidinylthiocarbapenem compound of formula I and its salts:

15

20



(wherein R is optionally substituted amino; R<sup>1</sup> is hydrogen or 1C to 5C allyl; R<sup>2</sup> is hydrogen or a conventional hydroxy protective group; R<sup>3</sup> is hydrogen or an imino protective group or imino substituent; R<sup>4</sup> is 1C to 5C alkylene; and R<sup>5</sup> is hydrogen or a conventional carboxy protective group; and wavy lines each shows a bond in R or S configuration).

25 2. A compound claimed in Claim 1 wherein the stereochemistry in the pyrrolidine ring is either in (2S,4R) or (2S,4S)-configuration.

30 3. A compound claimed in Claim 1 wherein R<sup>1</sup> is methyl.

4. A compound claimed in Claim 1 wherein R<sup>4</sup> is methylene.

35 5. A compound claimed in Claim 1 wherein R<sup>2</sup> is hydrogen or tri-1C to 4C alkylsilyl.

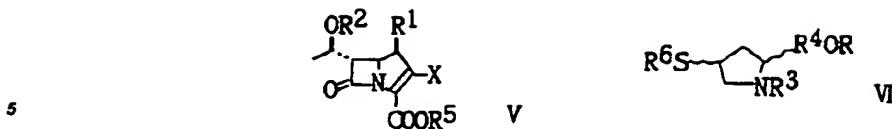
6. A compound claimed in Claim 1 wherein R<sup>3</sup> is hydrogen.

7. A compound claimed in Claim 1 wherein R<sup>5</sup> is hydrogen or alkali metal.

40 8. A compound claimed in Claim 1 wherein R is methanesulfonylamino, or sulfamoylamino.

9. A compound claimed in Claim 1 wherein  
R is amino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;  
R is acetylarnino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;  
R is carbomethoxyarnino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;  
R is methylcarbamoylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;  
R is methanesulfonylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;  
R is sulfamoylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;  
R is methylarnino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen; or  
R is ethylidenearnino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;  
or its alkali metal salt, provided that its stereochemistry at the pyrrolidine ring is (2S,4R)- or (2S,4S)-.

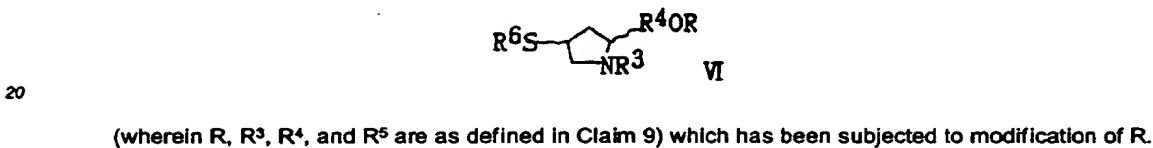
55 10. A process for preparing a compound claimed in Claim 1 which comprises treating a carbapenem V or its reactive derivative with a thiol VI (R<sup>6</sup> is hydrog n) or its reactive derivative:



(wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are as defined in Claim 1, R<sup>6</sup> is hydrogen or a thiol protective group, and X is a leaving group) and, if required, followed by removing of a protective group at R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and/or R<sup>5</sup>.

11. The process as claimed in Claim 9 wherein the product is subjected to modification at R or introduction of R<sup>3</sup>.

15 12. The thiol of formula VI:



13. A pharmaceutical formulation containing a compound claimed in any one of claims 1 to 9 as an active ingredient.

25 14. A pharmaceutical formulation according to Claim 13 which is useful as an antibacterial agent.

**Claims for the following Contracting State : GR**

30 1. An aminoxyppyrrolidinylthiocarbapenem compound of formula I and its salts:



40 (wherein R is optionally substituted amino; R<sup>1</sup> is hydrogen or 1C to 5C allyl; R<sup>2</sup> is hydrogen or a conventional hydroxy protective group; R<sup>3</sup> is hydrogen or an imino protective group or imino substituent; R<sup>4</sup> is 1C to 5C alkylene; and R<sup>5</sup> is hydrogen or a conventional carboxy protective group; and wavy lines each shows a bond in R or S configuration).

45 2. A compound claimed in Claim 1 wherein the stereochemistry in the pyrrolidine ring is either in (2S,4R) or (2S,4S)-configuration.

3. A compound claimed in Claim 1 wherein R<sup>1</sup> is methyl.

4. A compound claimed in Claim 1 wherein R<sup>4</sup> is methylene.

50 5. A compound claimed in Claim 1 wherein R<sup>2</sup> is hydrogen or tri-1C to 4C alkylsilyl.

6. A compound claimed in Claim 1 wherein R<sup>3</sup> is hydrogen.

7. A compound claimed in Claim 1 wherein R<sup>5</sup> is hydrogen or alkali metal.

55 8. A compound claimed in Claim 1 wherein R is methanesulfonylamino, or sulfamoylamino.

9. A compound claimed in Claim 1 wherein

R is amino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;  
 R is acetylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;  
 R is carbomethoxyamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;

5 R is methylcarbamoylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;

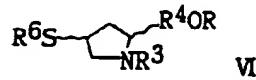
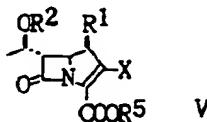
R is methanesulfonylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;

10 R is sulfamoylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;  
 R is methylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen; or

15 R is ethylideneamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen; or its alkali metal salt, provided that its stereochemistry at the pyrrolidine ring is (2S,4R)- or (2S,4S)-.

10. A process for preparing a compound claimed in Claim 1 which comprises treating a carbapenem V or its reactive derivative with a thiol VI (R<sup>6</sup> is hydrogen) or its reactive derivative:

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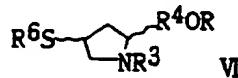
(wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are as defined in Claim 1, R<sup>6</sup> is hydrogen or a thiol protective group, and X is a leaving group) and, if required, followed by removing of a protective group at R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and/or R<sup>5</sup>.

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11. The process as claimed in Claim 9 wherein the product is subjected to modification at R or introduction of R<sup>3</sup>.

12. The thiol of formula VI:

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(wherein R, R<sup>3</sup>, R<sup>4</sup>, and R<sup>6</sup> are as defined in Claim 9) which has been subjected to modification of R.

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13. A method for the preparation of a pharmaceutical composition comprising combining a compound according to any one of claims 1 to 9 with a pharmaceutically acceptable carrier.

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14. The method according to Claim 13 wherein the pharmaceutical composition prepared is useful as an antibacterial agent.

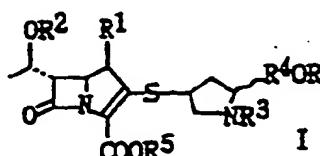
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**Claims for the following Contracting State : ES**

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1. A process for preparing an aminooxypyrrolidinylthiocarbapenem compound of formula I and its salts:

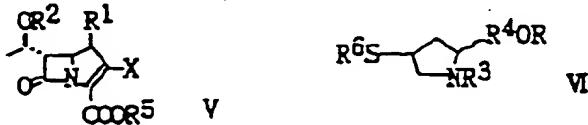
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(wherein R is optionally substituted amino; R<sup>1</sup> is hydrogen or 1C to 5C alkyl; R<sup>2</sup> is hydrogen or a conventional hydroxy protective group; R<sup>3</sup> is hydrogen or an imino protective group or imino substituent; R<sup>4</sup> is 1C

to 5C alkylene; and R<sup>5</sup> is hydrogen or a conventional carboxy protective group; and wavy lines each shows a bond in R or S configuration) which comprises treating the carbapenem V or its reactive derivative with the thiol VI (R<sup>6</sup> is hydrogen) or its reactive derivative:

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(wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are as defined above, R<sup>6</sup> is hydrogen or a thiol protective group, and X is a leaving group) and, if required, followed by removing of a protective group at R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and/or R<sup>5</sup>.

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2. The process as claimed in Claim 1 wherein the product is subjected to modification at R or introduction of R<sup>3</sup>.

3. A process according to Claim 1 wherein the stereochemistry in the pyrrolidine ring of the compound prepared is either in (2S,4R) or (2S,4S) configuration.

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4. A process according to Claim 1 wherein R<sup>1</sup>, in the compound prepared, is methyl.

5. A process according to Claim 1 wherein R<sup>4</sup>, in the compound prepared, is methylene.

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6. A process according to Claim 1 wherein R<sup>2</sup>, in the compound prepared, is hydrogen or tri-1C to 4C alkylsilyl.

7. A process according to Claim 1 wherein R<sup>3</sup>, in the compound prepared, is hydrogen.

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8. A process according to Claim 1 wherein R<sup>5</sup>, in the compound prepared, is hydrogen or alkali metal.

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9. A process according to Claim 1 wherein R, in the compound prepared, is methanesulfonylamino or sulfamoylamino.

10. A process according to Claim 1 wherein, in the compound prepared, R is amino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;

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R is acetylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;

R is carbomethoxyamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;

R is methylcarbamoylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;

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R is methanesulfonylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;

R is sulfamoylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;

R is methylamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen; or

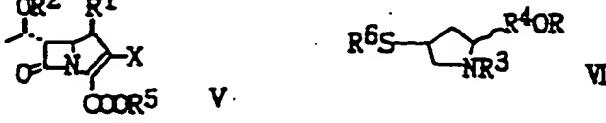
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R is ethylideneamino, R<sup>1</sup> is methyl, R<sup>2</sup> and R<sup>3</sup> are hydrogens, R<sup>4</sup> is methylene, and R<sup>5</sup> is hydrogen;

or its alkali metal salt, provided that its stereochemistry at the pyrrolidine ring is (2S,4R)- or (2S,4S)- which

comprises treating the carbapenem V or its reactive derivative with the thiol VI (R<sup>6</sup> is hydrogen) or its reactive derivative:

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(wherein R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, and R<sup>5</sup> are as defined above, R<sup>6</sup> is hydrogen or a thiol protective group, and X is a leaving group) and, if required, followed by removing of a protective group at R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and/or R<sup>5</sup>.

R<sup>6</sup>.

11. A method for the preparation of a pharmaceutical composition comprising combining a compound prepared according to any one of claims 1 to 10 with a pharmaceutically acceptable carrier.
- 5 12. A method according to claim 11 wherein the pharmaceutical composition is useful as an antibacterial composition.

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## EUROPEAN SEARCH REPORT

Application Number

EP 92 11 1356

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. CL.5)						
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim							
A	EP-A-0 341 557 (FUJISAWA PHARMACEUTICAL CO., LTD.) * claims *	1-14	C07D477/00 C07D207/12 A61K31/40						
A	EP-A-0 272 456 (FUJISAWA PHARMACEUTICAL CO., LTD.) * claims *	1-14							
A	EP-A-0 182 213 (SUMITOMO PHARMACEUTICALS CO., LTD.) * claims *	1-14							
D,A	EP-A-0 280 771 (FUJISAWA PHARMACEUTICAL CO., LTD.) * claims *	1-14							
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			TECHNICAL FIELDS SEARCHED (Int. CL.5)						
			C07D A61K						
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>28 SEPTEMBER 1992</td> <td>CHOULY J.</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	28 SEPTEMBER 1992	CHOULY J.
Place of search	Date of completion of the search	Examiner							
THE HAGUE	28 SEPTEMBER 1992	CHOULY J.							
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document							
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